

BUPRENORPHINE FORMULATIONS FOR CHRONIC PAIN MANAGEMENT IN PATIENTS WITH OPIOID USE DISORDER OR ON LONG-TERM OPIOID THERAPY WITH PHYSIOLOGIC TOLERANCE

Buprenorphine Inj, Buprenorphine TDS, Buprenorphine SL Film, Buprenorphine/Naloxone SL tabs Recommendations for Use

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VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives; National Mental Health Office – Substance Use Disorders; National Pain Management Strategy Coordinating Committee

The following recommendations are based on medical evidence, clinician input, and expert opinion. The content of the document is dynamic and will be revised as new information becomes available. Local adjudication should be used until updated guidance and/or CFU are developed by the National PBM. The purpose of this document is to assist practitioners in clinical decision-making, to standardize and improve the quality of patient care, and to promote cost-effective drug prescribing.

The Product Information should be consulted for detailed prescribing information.

Pharmacotherapeutic Considerations on the use of Buprenorphine for Pain Management

NOTE: Main purpose for current revision is to update RFU so guidance document is consistent with the removal of the DATA-2000/X-waiver requirement as per the “Consolidated Appropriations Act, 2023 Sec 1262”. Additional updates planned for late 2023.

Introduction

Buprenorphine is an opioid with formulations approved for Opioid Dependence (as per ICD-10) or Opioid Use Disorder (OUD) (as defined by DMS-5) and with formulations approved for pain management. Regarding its pain indication, it is approved for chronic pain in buccal and transdermal dosage forms, and for acute pain in injectable form. The injectable formulation of buprenorphine (Buprenex®, BUP INJ) was approved in 1985 in the United States for acute pain management. Since then, two other formulations have been approved with indications for pain severe enough to require daily, around-the-clock, long-term opioid treatment, specifically buprenorphine transdermal (Butrans®, BUP TDS) and buprenorphine buccal film (Belbuca®, BUP BF). In addition, the buprenorphine-naloxone combination product (Suboxone®, BUP/NAL) and the buprenorphine sublingual tablet (Subutex®, BUP) that are approved for Opioid Dependence (ICD-10)/OUD are being advocated off-label for pain management (Table 1).

This Recommendations for Use (RFU) document is intended to provide guidance on the use of buprenorphine, in its different formulations, for pain management, including for patients at high risk from other opioids due to medical or mental health factors and specifically also for patients who have comorbid Opioid Dependence (as defined by ICD-10) or OUD and chronic pain conditions.

ICD-10 F11.2x Opioid Dependence is characterized by a cluster of cognitive, behavioral, and physiological features. The presence of three or more of the following six features simultaneously at any one time in the preceding year indicates opioid dependence:

- a strong desire or sense of compulsion to take opioids
- difficulties in controlling opioid use (onset, termination or levels of use)
- a physiological withdrawal state
- tolerance
- progressive neglect of alternative interests because of opioid use
- persisting with opioid use despite clear evidence of overtly harmful consequences

According to ICD-10, opioid dependence does not develop without a period of regular use, although regular use alone is not sufficient to imply dependence.

DSM-5 Opioid Use Disorder (OUD) is characterized by a cluster of cognitive, behavioral, and physiological symptoms indicating that the individual continues using substances despite significant substance-related problems. The diagnosis is defined by meeting two or more of eleven criteria including:

- Opioids are often taken in larger amounts or over a longer period than was intended.
- There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
- Craving, or a strong desire or urge to use opioids.
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
- Important social, occupational, or recreational activities are given up or reduced because of opioid use.
- Recurrent opioid use in situations in which it is physically hazardous.
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
- Exhibits tolerance (see discussion in the next section).
- Exhibits withdrawal (see discussion in the next section).

According to DSM-5 OUD the criteria of tolerance and withdrawal do not count as OUD criteria in patients who are only taking opioids under appropriate medical supervision. DSM-IV included these symptoms, and like, ICD-10 required at least one other symptom of behavioral problems to make an “opioid dependence” diagnosis. However, the update in DSM-5 created a “mild” OUD category that requires only 2 criteria. The committee wanted to avoid diagnosing those with physiologic tolerance and withdrawal from taking opioids as prescribed as being diagnosed with OUD. Thus, they eliminated these two criteria for patients only taking opioids as prescribed. To meet DSM-5 criteria for OUD, such patients must manifest two or more symptoms such as opioid craving, difficulty tapering, taking more medication than intended, or continued use despite clear evidence of opioid-related harmful consequences. This has created DSM-5 “diagnostic orphans” who manifest opioid tolerance, withdrawal, and one other symptom of opioid-related behavioral problems. They do not meet DSM-5 opioid use disorder criteria; however, by ICD-10 definition, such patients have ICD-10 opioid dependence.

This ambiguity creates an opportunity for clinical judgement and shared decision-making between the patient and provider, but it is important that the appropriate diagnoses are documented, and that prescribing is consistent with federal law. The FDA-approved indication for BUP/NAL (Suboxone®) is “opioid dependence”. For a patient with ICD-10 Opioid Dependence (or DSM-5 Opioid Use Disorder) in the context of comorbid chronic pain, offering treatment with either BUP/NAL or methadone through an approved OAT program, allows treatment of opioid dependence (i.e., relieve withdrawal & prevent relapse, suicide, and overdose) and offers also potential benefit regarding pain management. BUP/NAL may be prescribed by any provider with an independent DEA license and there are no longer any limits on the number of patients a provider may treat.

NOTE: some States of licensure will have more stringent restrictions for prescribing of BUP/NAL and BUP. Prescribers should be familiar with their State of licensures regulations surrounding the prescribing for C-III controlled substances and Bup/NAL and BUP specifically.

Most patients with chronic pain who are on opioid therapy and who do not have ICD-10 Opioid Dependence (or DSM-5 OUD) will be able to slowly taper opioid pain medications, if clinically indicated due to risk outweighing the benefit, such as with high dose or in the context of sedatives including benzodiazepines. The rate needs to be individualized according to the VA/DoD Clinical Practice Guideline: Management of Opioid Therapy for Chronic Pain (<https://www.healthquality.va.gov>) and in the CDC 2022 CPG for Prescribing Opioids for Chronic Pain¹. A common approach for patients on long-term opioid therapy is a gradual reduction by 5-10% per month, but slower tapering may be better tolerated in some, including patients with very longstanding opioid therapy. For patients who have great difficulty with making any reduction in opioid medication even when risks seem to outweigh benefits, a diagnosis of ICD-10 opioid dependence should be considered. Patients who have tolerance, withdrawal and difficulty tapering satisfy the ICD-10 diagnostic criteria for Opioid Dependence. Nevertheless, not all patients with difficulty tapering their opioid medication, even at slow rate, have ICD-10 opioid dependence as opioid medication may be taken for the relief of pain more than what is prescribed, and the pain intensity be exacerbated transiently by opioid reduction. Thus, these patients must be carefully assessed for the most appropriate therapeutic approach. For patients with ICD-10 opioid dependence, a switch to BUP/NAL or BUP maintenance to treat both pain and opioid dependence/OUD is recommended and may be life-saving. An X-waiver is NO LONGER required to prescribe BUP/NAL or BUP for opioid dependence maintenance treatment. Note that strong evidence from multiple clinical trials and population-based case-control studies confirms that patients with opioid dependence have high mortality from all causes and better outcomes including reduced risk of premature death with maintenance medication treatment than with tapering.

Some patients with chronic pain controlled on long-term opioid therapy with no history or current evidence of ICD-10 opioid dependence or DSM-5 OUD may benefit from a switch to buprenorphine to mitigate the risk of mu opioid agonist pain medications. For example, a patient with sleep apnea and renal insufficiency who is at-risk for respiratory depression but also not a candidate for non-steroidal anti-inflammatory drugs. While it is legal to prescribe buprenorphine/naloxone “off-label” for treatment of pain, in practice patients on high-risk opioid pain regimens often meet the ICD-10 definition of opioid dependence and have this diagnosis on encounter forms in their record.

Patients with ICD-10 Opioid Dependence (or DSM-5 OUD) who are not doing well in Primary Care may be referred to addiction specialty or pain management teams such as the CARA (Comprehensive Addiction and Recovery Act of 2016) mandated Pain Teams. These interdisciplinary Pain Management Teams support Primary Care providers and include pain specialty providers for medical, behavioral, and rehabilitative pain care modalities while also integrating addiction medicine/psychiatry. Patients with OUD and co-morbid pain who are stabilized on BUP or BUP/NAL may be transitioned back to their primary care provider, via warm hand-off.

Buprenorphine Clinical Pharmacology in Pain Management

Pharmacologically, buprenorphine's primary effects are caused by its partial agonism of mu-opioid receptors (MORs) and antagonism at kappa-opioid receptors (KORs).² Although it has some, but lower, ability to bind to opioid receptor ligand (ORL)-1 (also known as nociceptin) and delta-opioid receptors (DORs), the clinical effects from these are negligible.³⁻⁷ Its traditional categorization as a partial agonist at MORs is primarily due to its lower intrinsic activity (the biological stimulus a drug has on a receptor) compared to full MOR agonists, as shown mainly in *in vitro* binding receptor assay studies.¹⁻⁶ This categorization, however, should not be confused with measures of relative clinical efficacy and potency for analgesia. Several clinical studies have shown that at low to moderate doses, buprenorphine can elicit similar analgesic effects compared to equivalent doses of full

MOR agonists.⁸⁻¹⁶ Its partial agonistic activity on MORs and antagonistic activity on KORs does allow for a plateauing of the dose response curve (or ceiling effect) regarding retention of carbon dioxide (as a marker for respiratory depression), thus lowering the risk of overdose when used without other central nervous system (CNS) depressants.¹⁶⁻¹⁸

Buprenorphine also has one of the highest binding affinities toward MORs compared to all other opioids, the only exception being naltrexone.¹⁹⁻²⁰ This strong binding allows buprenorphine to preferentially occupy available MORs thereby disallowing full agonist opioids to bind, and while this is not a displacement per se, the net effect causes reversal of opioid activity.²¹⁻²² It also has an extremely slow dissociation rate (the measure of disengagement from the target receptor) from MORs; thus once bound, it is not easily nor quickly displaced.⁶

For more information on the clinical pharmacology of buprenorphine, see the [Buprenorphine Perioperative Guidance Supplemental Information](#).

VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain

The [VA/DoD Clinical Practice Guideline for Opioid Therapy for Chronic Pain](#) recommends against initiation of long-term opioid therapy for chronic pain. In all cases non-opioid and non-pharmacologic alternatives for pain management must be part of the treatment plan. For patients on long-term opioid therapy without ICD-10 opioid dependence or OUD, slowly tapering opioids can be an important strategy to reduce the risks of OUD and overdose death and is recommended, if risks outweigh benefits, in a patient-centered individualized approach.

Because of the high morbidity and mortality associated with ICD-10 Opioid dependence/DSM-5 Opioid Use Disorder and the effectiveness of Medication for OUD (MOUD, previously referred to as Medication Assisted Therapy (MAT)) in reducing morbidity and mortality in such patients, providers should be prepared to provide long-term treatment with buprenorphine in those patients with ICD-10 opioid dependence or DSM-5 OUD. Patients on long-term use of opiate analgesics for chronic pain are a heterogeneous population with diverse medical, mental health, and Substance Use Disorder comorbidities; buprenorphine product and dosing selection should be selected based on the individual patient needs.

Buprenorphine Dose Equivalence to Morphine

There is wide variability in the reported buprenorphine to morphine equianalgesic ratios with estimated ratios between 1:10 and 1:100.^{23, 24} The Opioid Therapy Risk Report (OTRR) and OSI Dashboard use conversion ratios based on the Centers for Medicare and Medicaid Services (CMS) and Center for Disease Control (CDC) conversion tables.^{24, 1} The conversion factor for the patch is based on a 1:75 buprenorphine: morphine equivalency. Use of this ratio when converting from oral morphine to BUP TDS would result in a TDS dose that is higher than that recommended in the TDS prescribing information (PI).²⁴ For example, 30mg of morphine per day/75 = 0.4mg of BUP/day, divided by 24 hours = 16mcg BUP TDS; the BUP TDS PI recommends a 10mcg patch for 30mg of morphine. We recommend following the BUP TDS prescribing information guidance understanding that the recommended BUP TDS conversion ratio is very conservative, and the patient may require supplemental analgesia for breakthrough pain during initial conversion to the patch.

While a ratio of 0.4 mg SL buprenorphine to 30 mg of immediate-release morphine has been proposed, the OSI Dashboard has been using a 1:10 buprenorphine: morphine ratio based on prior CMS and CDC tables.^{23, 25} The CMS and the CDC are no longer making any dose equivalency recommendations for buprenorphine: morphine.²⁶ Given the wide variability in the recommended dose equivalencies between buprenorphine and morphine, we are unable to make any recommendations for equianalgesic dosing.

Table 1. Buprenorphine products for Pain Management

Formulary Buprenorphine Products					
Generic Name	Brand Name	Formulation	FDA-Approved Indications	Bioavailability	Elimination Half-Life
Buprenorphine	Butrans® (VANF)	Transdermal delivery system Available in 5, 7.5, 10, 15 and 20 mcg/hr patches	Management of pain severe enough to require around-the-clock, long-term opioid treatment	~15%	~26 hours

		Max dose: 20 mcg/hr every week			
Buprenorphine	Belbuca® (VANF)	Buccal film Available in 75, 150, 300, 450, 600, 750, 900 mcg films Max dose: 900 mcg every 12 hours	Management of pain severe enough to require around-the-clock, long-term opioid treatment	46 to 65%	11.2 to 27.6 hours
Buprenorphine and naloxone	Suboxone® (VANF)	Sublingual tablet and film Available in 2-0.5 and 8-2 mg SL tabs and 2-0.5, 4-1, 8-2, and 12-3 mg film Target maintenance dose for OUD is 16 – 24mg/day	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab) ~36% (film)*	24 to 42 hours
Buprenorphine	Subutex® (VANF)	Sublingual tablet Available in 2mg and 8 mg SL tablets Target maintenance dose for OUD is 16 – 24mg/day	Used off-label for pain management. FDA approved for the treatment of opioid dependence (a.k.a. ICD-10 F11.2x opioid dependence or DSM-5 OUD).	~30% (tab)	24 to 42 hours
Non-Formulary Buprenorphine Products					
Buprenorphine	Buprenex® (NF)	IM, IV Available in 0.3 mg/ml ampules Dosing: 0.3 mg every 6-8 hours as needed	Indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.	100%	1.2-7.2 hours (mean 2.2 hours)

- The bioavailability (AUC) of buprenorphine is about 20% greater for buprenorphine with naloxone 8 mg / 2 mg sublingual film than for the corresponding tablets; but this may not be clinically important for many patients.²⁷

Buprenorphine Injection (BUP INJ). Intended for intramuscular (IM) or intravenous (IV) administration in the acute setting, BUP INJ was the first buprenorphine product for pain management, launched in the United States in 1985, and indicated for the management of pain severe enough to require an opioid analgesic and for which alternate treatments are inadequate.^{28,29} It contains 0.3mg of buprenorphine per 1ml of solution. There are insufficient data to recommend single doses greater than 0.6mg and the maximum recommended adult dose is 0.6mg administered in 6-hour intervals. BUP INJ is not FDA-approved for treatment of opioid dependence/OD.

Buprenorphine TDS (BUP TDS). BUP TDS is available in 5, 7.5, 10, 15, and 20 mcg/hour patches; the BUP TDS prescribing information recommends the 5mcg/hr patch as the starting dose for patients on less than 30mg oral morphine equivalents per day while the 10mcg patch is the recommended starting dose for patients on 30-80 mg of daily morphine equivalents.³⁰ These patients must be tapered to 30mg oral morphine equivalent prior to initiating therapy with BUP TDS 10 mcg/hour. Dose adjustments should not be made until at least 72 hours of use at the same strength since it takes approximately 72 hours to achieve steady state

concentrations. BUP TDS has an apparent terminal half-life of 26 hours. BUP TDS may be a viable option in those patients who cannot tolerate the oral route of administration, as well as in the geriatric population who are more susceptible to the adverse reactions related to other opioids. BUP TDS may also be a good option for use in patients where there are concerns with the prescription of oral opioids. BUP TDS may not provide adequate analgesia for patients requiring greater than 80 mg of morphine equivalents per day. BUP TDS is not FDA-approved for treatment of opioid dependence/OD.

Buprenorphine Buccal Film (BUP BF). BUP BF is available in 75 mcg, 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg dosage strengths. Opioid-naïve patients may be started at 75 mcg once daily or every 12 hours but starting doses for the opioid-experienced patient are based on the daily morphine equivalent dose when converting from other opioids to BUP BF. As with BUP TDS and per BUP BF prescribing information, patients must be tapered to 30mg oral morphine equivalent or less prior to initiating therapy with BUP BF. Two 12-week, multicenter, Phase III studies, one in opioid-naïve and one in opioid-experienced patients, were able to demonstrate statistically significant reductions in pain scores in patients with chronic low back pain with BUP BF when compared with placebo.^{31,32} BUP BF may not provide adequate analgesia for patients requiring greater than 160 mg oral Morphine equivalent daily dose (MEDD); consider the use of an alternate analgesic.³³ BUP BF is not FDA-approved for treatment of opioid dependence/OD.

Buprenorphine (BUP) and Buprenorphine/Naloxone (BUP/NAL). BUP/NAL was approved by the FDA in 2002 for treatment of opioid dependence (a.k.a. DSM-5 OUD)²⁷ but is sometimes prescribed off-label for chronic pain management.³⁴ Possible mechanisms for pain relief by BUP/NAL include reversal of opioid induced-hyperalgesia and improvement in opioid dependence symptoms.^{23,34, 35} One randomized controlled clinical trial demonstrated the efficacy of BUP/NAL for pain management in patients being treated for opioid use disorder (OUD).³⁶ Current data suggest that buprenorphine may provide pain relief in patients with chronic pain and opioid use disorder, but the data for patients without opioid use disorder or addiction are insufficient to guide safe and appropriate use.³⁴⁻⁴¹ A Cochrane meta-analysis found buprenorphine superior to other opioids (5 out of 11 studies), equivalent (3 out of 11 studies) or inferior to the alternative treatment (3 out of 11 studies) for pain relief in cancer.³⁸ The evidence for all the outcomes in this meta-analysis was considered very low quality. One systematic review which included 10 trials involving 1,190 patients reported that, while all studies demonstrated that sublingual buprenorphine showed some effectiveness as a chronic pain analgesic, the majority of studies were observational and of low quality.³⁹ A retrospective cohort study in a VHA hospital Opioid Reassessment Clinic (ORC) demonstrated the feasibility of rotating patients on long-term opioid therapy for pain to BUP/NAL.⁴¹ Further research is needed to demonstrate the efficacy of BUP/NAL for pain in patients with and without opioid dependence/OD.

Split dosing. Substance Abuse and Mental Health Services Administration (SAMHSA), the American Society of Addiction Medicine (ASAM), and the VA/DoD support the use of buprenorphine for both pain and OUD in patients receiving buprenorphine for treatment of opioid use disorder and who develop or have a pain condition severe enough to require an opioid analgesic.^{37,42,43} These clinical guidelines suggest splitting the dose for twice or three times daily administration for pain management.

Z79.891 ICD-10 Long term (current) use of opioid analgesic versus F11.2 ICD-10 Opioid Dependence/DSM-5 Opioid Use Disorder (OUD). For patients without opioid dependence/OD but who have chronic pain and physiologic tolerance to opioids, the primary diagnosis would be the painful condition. If the focus of the encounter is only management of opioid use, then it is appropriate to add ICD-10 Z79.891, Long term (current) use of opiate analgesic. Most patients with pain and Z79.891 would be able to slowly taper opioid analgesics (such as by 5% to 10% per month, or slower in an individualized approach) if the opioid risks outweigh the benefits.

Patients who experience tolerance leading to inadequate pain control, no evidence of improvement in functional status, opioid withdrawal symptoms, and difficulty tapering or discontinuing opioids even when the risks clearly outweigh the benefits, and the tapering regimen is optimized would meet the ICD-10 definition of opioid dependence and treatment with buprenorphine for both opioid dependence and pain would be indicated. More information on the diagnosis and management of Opioid Use Disorder is available in the OUD Clinician's Guide from VA's Academic Detailing Service at this URL:
<https://vawww.portal2.va.gov/sites/ad/SitePages/OD.aspx>

Additional Considerations

QTc Monitoring. Buprenorphine mildly inhibits cardiac repolarization and has been noted to prolong the QT interval when the transdermal patch is administered at doses greater than 20mcg/hour.^{23,30} Per BUP TDS prescribing information, the effect of BUP TDS 10 mcg/hour and 2 x BUTRANS 20 mcg/hour on QTc interval was evaluated in a double-blind (BUP TDS vs. placebo),

randomized, placebo and active-controlled (moxifloxacin 400 mg, open label), parallel-group, dose-escalating, single-dose study in 132 healthy male and female subjects aged 18 to 55 years. There was no clinically meaningful effect on mean QTc with a BUTRANS dose of 10 mcg/hour. A BUTRANS dose of 40 mcg/hour (given as two 20 mcg/hour BUTRANS Transdermal Systems) prolonged mean QTc by a maximum of 9.2 (90% CI: 5.2-13.3) msec across the 13 assessment time points. Despite this finding, there has not been a concern to monitor buprenorphine with serial ECGs in the maintenance literature nor are there any recommendations for ECG monitoring for SL BUP or BUP/NAL.^{23,27} However, consider the potential for QTc prolongation in patients with hypokalemia, severe hypomagnesemia, or clinically unstable cardiac disease and consider avoiding the use of SL BUP in patients with a history of Long QT Syndrome, family history of Long QT Syndrome, or those taking Class IA or Class III antiarrhythmic drugs or combining with drugs that are known to prolong the QT interval.³⁰

Table 2 BUPRENORPHINE PAIN MANAGEMENT GUIDANCE FOR CHRONIC PAIN^{27,29,30,33,44} (See Appendix A for Buprenorphine for Pain Management Algorithm).

Topic	BUP TDS (BUTRANS)	BUP Buccal Film (BF) (BELBUCA)	BUP and BUP/NAL (SUBOXONE, generics)
Recommended Conditions for Use in Pain Management	<p>Indication is management of moderate to severe chronic pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time</p> <p>AND</p> <p>The patient is assessed as high risk for traditional oral opioid therapy and alternate buprenorphine products are not advisable.</p> <p>OR</p> <p>Patient has documented difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting).</p> <p>BUP TDS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic or, if buprenorphine is required, consider the use of BUP BF.</p>	<p>Indication is management of moderate to severe chronic pain requiring a continuous, around-the-clock opioid analgesic for an extended period of time</p> <p>AND</p> <p>The patient is assessed as high risk for traditional oral opioid therapy and alternate buprenorphine products are not advisable.</p> <p>OR</p> <p>Patient has documented difficulty swallowing, poor or unpredictable gastrointestinal absorption (e.g., short bowel; nausea, vomiting).</p> <p>BUP BF may not provide adequate analgesia for patients requiring greater than 160 mg/day oral morphine equivalents. Consider the use of an alternate analgesic or, if buprenorphine is required, consider referral to an x-waivered provider for consideration of buprenorphine or buprenorphine/naloxone Sublingual tablet.</p>	<p>BUP and BUP/NAL SL tablets are indicated for the induction and maintenance treatment of opioid dependence (ICD-10, a.k.a. OUD).</p> <p>BUP and BUP/NAL may be used by any DEA licensed provider for pain management and comorbid opioid dependence/OD.</p>
Considerations for Use	<ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with 	<ul style="list-style-type: none"> Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with 	

	<p>extended-release opioid formulations, reserve BUP TDS for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.</p> <ul style="list-style-type: none"> • BUP TDS is not indicated as an as-needed (prn) analgesic. • Instruct patients to wear BUP TDS for 7 days and to wait a minimum of 3 weeks before applying to the same site. • Do not abruptly discontinue BUP TDS in a physically dependent patient. • Allow 3 days on current dose to evaluate the full therapeutic effect prior to making additional dosage adjustments • Do not apply direct heat 	<p>extended-release opioid formulations, reserve BUP BF for use in patients for whom alternative treatment options (e.g., non-opioid analgesics or immediate-release opioids) are ineffective, not tolerated, or would be otherwise inadequate to provide sufficient management of pain.</p> <ul style="list-style-type: none"> • BUP BF is not indicated as an as-needed (prn) analgesic. • To be prescribed only by health care providers knowledgeable in use of potent opioids for management of chronic pain. • Use the lowest effective dosage for the shortest duration consistent with individual patient treatment goals • Individualize dosing based on the severity of pain, patient response, prior analgesic experience, and risk factors for addiction, abuse, and misuse 	<p>BUP sublingual tablet contains no naloxone and may be preferred during pregnancy, BUP/NAL sublingual tablet is preferred for most patients, but especially if there are concerns for misuse or diversion.</p> <ul style="list-style-type: none"> • If used for pain in a patient without ICD-10 opioid dependence, the encounter should indicate the pain condition diagnosis, the prescription should state “for pain management”.
Baseline Evaluation	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Monitor for effectiveness of pain relief Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Monitor for effectiveness of pain relief or prevention of opioid withdrawal symptoms Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>	<p>Urine drug screen (UDS) Prescription Drug Monitoring Program (PDMP) Check Liver transaminases Urine beta-HCG for females Monitor for effectiveness of pain relief or prevention of opioid withdrawal symptoms Assess patient's risk for physical or psychological dependence, drug diversion and sensitivity to adverse effects, particularly respiratory depression Assess mental status, respiratory status, and increased risk for falls.</p>
Dosage and Administration	<p>BUP TDS doses of 7.5, 10, 15, and 20 mcg/hour are for opioid experienced patients only. For opioid-naïve patients, initiate with a 5 mcg/hour patch. Each BUP TDS patch is intended to be worn for 7 days. <u>Conversion from Other Opioids to BUP TDS</u></p>	<p>BUP BF is for oral buccal use only and is to be applied to the buccal mucosa every 12 hours. Discontinue all other around-the-clock opioid drugs when BUP BF therapy is initiated. <i>For the Opioid-Naïve or Opioid Non-Tolerant patient.</i></p> <ul style="list-style-type: none"> • Initiate treatment in opioid-naïve and opioid-non-tolerant patients with a 75 mcg film once daily or, if 	<p><u>For patients on BUP/NAL for ICD-10 opioid dependence/ OUD.</u> The current 24-hour dose of BUP/NAL can be split and divided for BID or TID dosing for pain management. <u>When initiating BUP/NAL for patients who do not meet ICD-10 definition of opioid dependence but who are not appropriate for BUP TDS or BUP BF.</u></p>

	<ul style="list-style-type: none"> Discontinue all other around-the-clock opioid drugs when BUP TDS therapy is initiated. There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. <p><i>Prior Total Daily Dose of Opioid Less than 30 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> Initiate treatment with BUP TDS 5 mcg/hour at the next dosing interval <p><i>Prior Total Daily Dose of Opioid Between 30 mg to 80 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> Taper the patient's current around-the-clock opioids for up to 7 days or more as tolerated by the patient, to no more than 30 mg of morphine or equivalent per day before beginning treatment with BUP TDS. Then initiate treatment with BUP TDS 10 mcg/hour at the next dosing interval Patients may use short-acting analgesics as needed until analgesic efficacy with BUP TDS is attained. <p><i>Prior Total Daily Dose of Opioid Greater than 80 mg of Oral Morphine Equivalents per Day:</i></p> <ul style="list-style-type: none"> BUP TDS 20 mcg/hour may not provide adequate analgesia for patients requiring greater than 80 mg/day oral morphine equivalents. Consider the use of an alternate analgesic. <p>If the patient experiences problems with adhesion, the patch may be secured with a transparent adhesive film dressing such as Tegaderm™.</p>	<p>tolerated, every 12 hours for at least 4 days, then increase dose to 150 mcg every 12 hours.</p> <ul style="list-style-type: none"> Individual titration to a dose that provides adequate analgesia and minimizes adverse reactions should proceed in increments of 150 mcg every 12 hours, no more frequently than every 4 days. Doses up to 450 mcg every 12 hours were studied in opioid-naïve patients in the clinical trials; use of higher starting doses in patients who are not opioid tolerant may cause fatal respiratory depression. <p><i>Conversion from other Opioids to BUP BF</i></p> <ul style="list-style-type: none"> There is a potential for buprenorphine to precipitate withdrawal in patients who are already on opioids. To reduce the risk of opioid withdrawal, taper patients to no more than 30 mg oral MEDD daily before beginning BUP BF Initial BUP BF dose based on prior opioid expressed as oral MEDD <ul style="list-style-type: none"> Less than 30 mg oral MEDD ; BUP BF 75 mcg qd or q 12 hours 30 to 89 mg oral MEDD ; BUP BF 150 mcg q 12 hours 90 to 160 mg oral MEDD ; BUP BF 300 mcg q 12 hours > than 160 mg oral MEDD ; consider alternate analgesic. 	<p>Opioids should be discontinued the day prior, and the patient should be in mild withdrawal prior to initiation of BUP or BUP/NAL</p> <p>2mg to 4mg of BUP or 2mg/0.5mg to 4mg/1mg of BUP/NAL in divided doses should be adequate for most patients</p> <p>Alternatively, patients with moderate to severe withdrawal symptoms (COWS* score > 8) may require buprenorphine induction with stabilization at the lowest effective dose that controls withdrawal symptoms and minimizes side effects.</p> <p>The need for higher doses is determined by the pain and/or addiction specialists after thorough evaluation for efficacy and safety.</p> <p>*COWS = Clinical Opioid Withdrawal Scale.</p>
See individual product prescribing information for Contraindications, Warnings/Precautions, Dosing in Special Populations, Major and Common Adverse Effects, Drug Interactions, and monitoring.			
Discontinuation and tapering guidance	A decision to discontinue BUP TDS after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper at the	A decision to discontinue BUP BF after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper at the	A decision to discontinue SL BUP or BUP/NAL after a period of therapy should be part of a comprehensive treatment plan. There is insufficient data to determine the best method of dose taper

	end of treatment. For BUP TDS, it is reasonable to consider reducing the dose by 5mcg/hour every 2 to 4 weeks until the 7.5mcg/hour dose is reached; BUP TDS may be discontinued thereafter.	end of treatment. For BUP BF, as with other full mu agonists, it is reasonable to consider reducing the dose by 5 to 20% every 4 weeks for a slow taper, or 5 to 20% every week for a faster taper. See the Academic Detailing Opioid Taper Decision Tool for more guidance.	at the end of treatment. For SL BUP or BUP NAL, as with other full mu agonists, it is reasonable to consider reducing the dose by 5 to 10% every 4 weeks for a slow taper, or 15 to 20% every week for a faster taper. See the Academic Detailing Opioid Taper Decision Tool for more guidance.
Patient Education	<p>See BUP TDS Prescribing Information for full patient counselling guidance.</p> <p>Advise patients of the addiction, abuse and misuse potential of BUP TDS, the risks for life threatening respiratory depression, accidental exposure (especially in children), interaction with alcohol and other CNS depressants, risk for Neonatal Opioid Withdrawal Syndrome, side effects such as constipation, and caution with driving or operating heavy machinery.</p> <p>Advise patients on the proper administration and application of the patch, application site rotation, disposal, and to not apply direct heat.</p> <p>BUP TDS should be stored and kept out of sight and reach of children.</p>	<p>See BUP BF Prescribing Information for full patient counselling guidance.</p> <p>Advise patients of the addiction, abuse and misuse potential of BUP TDS, the risks for life threatening respiratory depression, accidental exposure (especially in children), interaction with alcohol and other CNS depressants, risk for Neonatal Opioid Withdrawal Syndrome, side effects such as constipation, and caution with driving or operating heavy machinery.</p> <p>Instruct patients how to properly use BUP BF, including the following:</p> <ul style="list-style-type: none"> • To carefully follow instructions for the application of BUP BF and to avoid eating or drinking until it dissolves. • Advise patients that, after BUP BF has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BUP BF before brushing teeth. Instruct patients to inform their dentist that they have started therapy on BUP BF. • To apply BUP BF once daily, or every twelve (12) hours at the same time or times each day. • To avoid applying BUP BF to areas of the mouth with any open sores or lesions. • To not use BUP BF if the pouch seal is broken or the buccal film is cut, damaged, or changed in any way. 	<p>See BUP and BUP/NAL Prescribing Information for full patient counselling guidance.</p> <p>Discuss methods to enhance medication adherence</p> <p>Negotiate patient's commitment to monitored ingestion</p> <p>The pill is taken once a day under the tongue, allow dissolving, do NOT chew or swallow.</p> <p>Store in secure place out of the reach of children.</p> <p>Adverse effects, if any, are usually mild and go away after the medication has been taken for a while. If you have side effects you should NOT abruptly stop taking your medication, instead, talk to your doctor about it.</p> <ul style="list-style-type: none"> • Advise patients that, after BUP or BUP/NAL has completely dissolved in the oral mucosa, to take a sip of water, swish it gently around their teeth and gums, and swallow. Advise patients to wait for at least one hour after taking BUP/NAL before brushing teeth. <p>Instruct patients to inform their dentist that they have started therapy on BUP/NAL</p>

		BUP BF should be stored and kept out of sight and reach of children.	
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References:

1. . Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022. MMWR Recomm Rep 2022;71(No. RR-3):1–95. [CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 | MMWR](#) Last Accessed February 24th, 2023
2. Chapter 18: Opioids, Analgesia,, and Pain Management. In: Hilal-Dandan R, Brunton LL, editors. Goodman and Gillman Manual of Pharmacology and Therapeutics. 2nd ED. McGraw Hill. New York, 2014.
3. Brown SM, Holtzman M, Kim T, Kharasch ED. Buprenorphine metabolites, buprenorphine-3-glucuronide and norbuprenorphine-3-glucuronide, are biologically active. Anesthesiology. 2011;115(6):1251-60.
4. Raffa RB, Haidery M, Huang HM, et al. The clinical analgesic efficacy of buprenorphine. J Clin Pharm Ther. 2014;39(6):577-83.
5. Huang P, Kehner GB, Cowan A, Liu-Chen LY. Comparison of pharmacological activities of buprenorphine and norbuprenorphine: norbuprenorphine is a potent opioid agonist. J Pharmacol Exp Ther. 2001;297:688–695.
6. Boas RA, Villiger JW. Clinical actions of fentanyl and buprenorphine. The significance of receptor binding. Br J Anaesth. 1985;57(2):192-6.
7. Sadee W, Rosenbaum JS, Herz A. Buprenorphine: differential interaction with opiate receptor subtypes in vivo. J Pharmacol Exp Ther. 1982;223(1):157-62.
8. Macintyre PE, Russell RA, Usher KA, Gaughwin M, Huxtable CA. Pain relief and opioid requirements in the first 24 hours after surgery in patients taking buprenorphine and methadone opioid substitution therapy. Anaesth Intensive Care. 2013;41(2):222-230.
9. Tigerstedt I, Tammisto T. Double-blind, multiple-dose comparison of buprenorphine and morphine in postoperative pain. Acta Anaesthesiol Scand, 1980;24:462–468.

10. Hovell BC, Ward AE. Pain relief in the post-operative period: a comparative trial of morphine and a new analgesic buprenorphine. *J Int Med Res*, 1977;5: 417–421.
11. Cuschieri RJ, Morran CG, McArdle CS. Comparison of morphine and sublingual buprenorphine following abdominal surgery. *Br J Anaesth*, 1984;56:855–859.
12. Gaitini L, Moskovitz B, Katz E, Vaisberg A, Vaida S, Nativ O. Sublingual buprenorphine compared to morphine delivered by a patient-controlled analgesia system as postoperative analgesia after prostatectomy. *Urol Int*, 1996;57:227–229.
13. Edge WG, Cooper GM, Morgan M. Analgesic effects of sublingual buprenorphine. *Anaesthesia*, 1979;34:463–467.
14. Bradley JP. A comparison of morphine and buprenorphine for analgesia after abdominal surgery. *Anaesth Intensive Care*, 1984;12:303–310.
15. Oifa S, Sydoruk T, White I et al. Effects of intravenous patient-controlled analgesia with buprenorphine and morphine alone and in combination during the first 12 postoperative hours: a randomized, double-blind, four-arm trial in adults undergoing abdominal surgery. *Clin Ther*, 2009;31:527–541.
16. Lehmann KA, Grond S, Freier J, Zech D. Postoperative pain management and respiratory depression after thoracotomy: a comparison of intramuscular piritramide and intravenous patient-controlled analgesia using fentanyl or buprenorphine. *J Clin Anesth*, 1991;3:194–201.
17. Dahan A, Yassen A, Bijl H, et al. Comparison of the respiratory effects of intravenous buprenorphine and fentanyl in humans and rats. *Br J Anaesth*. 2005;94(6):825-834.
18. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. *Br J Anaesth*. 2006;96(5):627-632.
19. Volpe DA, McMahon Tobin GA, Mellon RD, et al. Uniform assessment and ranking of opioid mu receptor binding constants for selected opioid drugs. *Regul Toxicol Pharmacol*. 2011;59(3):385-390.
20. Eissenberg T, Greenwald MK, Johnson RE, et al. Buprenorphine's physical dependence potential: antagonist-precipitated withdrawal in humans. *J Pharmacol Exp Ther*. 1996;276:449-459.
21. Bickel WK, Stitzer ML, Bigelow GE, Liebson IA, Jasinski DR, Johnson RE. Buprenorphine: dose-related blockade of opioid challenge effects in opioid dependent humans. *J Pharmacol Exp Ther*. 1988;247(1):47-53.
22. Strain EC, Walsh SL, Bigelow GE. Blockade of hydromorphone effects by buprenorphine/naloxone and buprenorphine. *Psychopharmacology (Berl)*. 2002;159(2):161-166.
23. Davis MP, Pasternick G, Behm B. Treating chronic pain: an overview of clinical studies centered on the buprenorphine option. *Drugs* 2018; 78: 1211-1228.
24. ML McPherson. *Demystifying Opioid Conversion Calculations*, 2nd Ed. ASHP, Bethesda, MA, 2018.
25. [CDC Clinical Practice Guideline for Prescribing Opioids for Pain — United States, 2022 | Table: Morphine](#) milligram equivalent doses for commonly prescribed opioids for pain management. [link](#) Accessed February 24, 2023
26. https://www.cdc.gov/drugoverdose/data-files/CDC_Oral_Morphine_Milligram_Equivalents_Sept_2018.xlsx Accessed May 2019
27. Suboxone™ [package insert]. Reckitt Benckiser Pharmaceuticals, Inc. Richmond, VA, 2011.
28. Campbell ND, Lovell AM. The history of the development of buprenorphine as an addiction therapeutic. *Ann NY Acad Sci* 2012; 1248: 124-139.
29. Buprenex™ [package insert] Indivior Inc., North Chesterfield, VA, January 2018.
30. Butrans™ [package insert]. Purdue Pharma L.P., Stamford, CT, 2014.
31. Gimbrel J, Spierings EL, Katz N, Xiang Q, et al. Efficacy and tolerability of buccal buprenorphine in opioid-experienced patients with moderate to severe chronic low back pain: results of a phase 3, enriched enrollment, randomized withdrawal study. *Pain* 2016; 157: 2517-2526.
32. Rauck RL, Potts J, Xiang Q, Tzanis E, et al. Efficacy and tolerability of buccal buprenorphine in opioid-naïve patients with moderate to severe chronic low back pain. *Postgrad Med* 2016; 128: 1-11.
33. Belbuca™ [package insert]. Endo Pharmaceuticals Inc., Malvern, PA, December, 2015.
34. Chen KY, Chen L, Mao J. Buprenorphine-naloxone therapy in pain management. *Anesthesiology* 2014; 120: 1262-74.
35. Daitch D, Daitch J, Novinson D, Frey M, et al. Conversion from high-dose full-opioid agonist to sublingual buprenorphine reduces pain scores and improves quality of life for chronic pain patients. *Pain Medicine* 2014; 15: 2087-94.
36. Neumann AM, Blondel RD, Jaanimagi U, Giambrone AK, et al. A preliminary study comparing methadone and buprenorphine in patients with chronic pain and co-existent opioid addiction. *J addict Dis* 2013; 32: 68-78.
37. TIP 54: Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders [Managing Chronic Pain in Adults With or in Recovery From Substance Use Disorders \(samhsa.gov\)](#) Accessed February 24, 2023
38. Schmidt-Hansen M, Bromham N, Taubert M et al. Buprenorphine for Treating Cancer Pain (Review). *Cochrane Database Syst Rev* 2015 Mar 31;(3): CD009596
39. Cote J, Montgomery L. Sublingual buprenorphine as an analgesic in chronic pain: a systematic review. *Pain Medicine* 2014; 15: 1171-8.
40. Berland DW, Malinoff HL, Weiner MA, Przybylski R. When opioids fail in chronic pain management: the role of buprenorphine and hospitalization. *Am J Therap* 2013; 20: 316-21.
41. Oldfield BJ, Edens EL, Agnoli A, Bone CW, et al. Multimodal treatment options, including rotating to buprenorphine, within a multidisciplinary pain clinic for patients on risky opioid regimens: a quality improvement study. *Pain Medicine* 2018; 19: S38-S45.

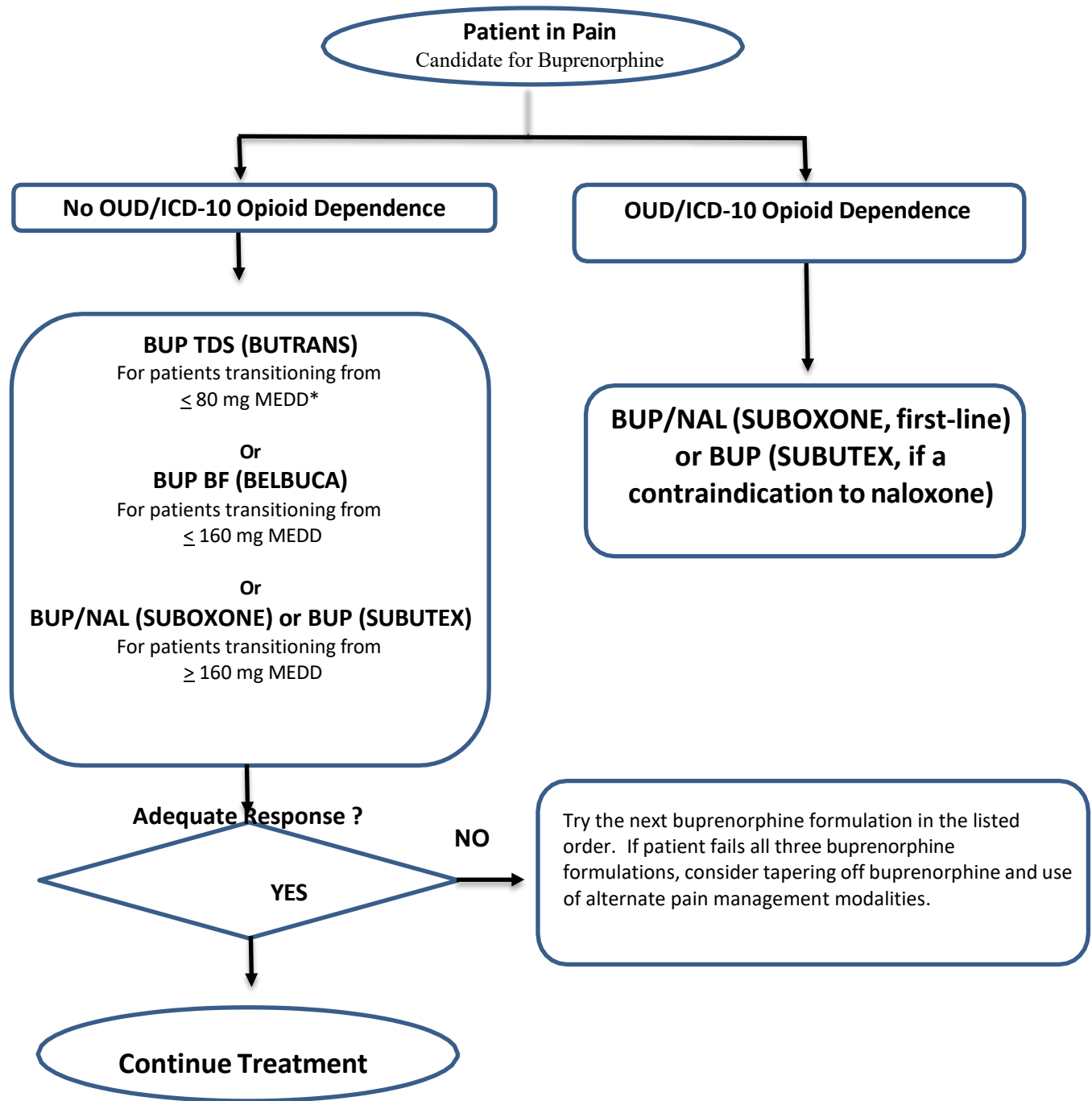
www.asam.org/docs/default-source/practice-support/guidelines-and-consensus-docs/asam-national-practice-guideline-supplement.pdf. Accessed on January 29, 2019

43. VA/DoD Clinical Practice Guideline for the Management of Substance Use Disorders.
[VA DoD Clinical Practice Guideline for the Management of Substance Use Disorders](#) Accessed February, 24, 2023
44. Lexicomp.Version 4.2.1., Wolters Kluwer Clinical Drug Information, Inc., Hudson, OH 2019.

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Appendix A



*Abbreviations: MEDD = Morphine Equivalent Daily Dose, BUP = Buprenorphine, BUP/NAL = Buprenorphine/Naloxone, BUP TDS = Buprenorphine Transdermal System, BUP BF = Buprenorphine Buccal Film, OUD = Opioid Use Disorder, ICD = International Classification of Diseases.